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Bladder cancer and drinking water: a population-based case-control study in Washington County, Maryland (United States)

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A population-based case-control study was conducted in Washington County, Maryland (United States) to explore the association between incident bladder cancer and exposure to drinking water from chlorinated surface sources. Cancer cases were White residents, enumerated in a 1975 county census and reported to the Washington County Cancer Registry (n = 294) between 1975 and 1992. White controls, frequency matched by age (± 5 years) and gender, were selected randomly from the census (n = 2,326). Households receiving municipal water, which generally derived from chlorinated surface waters, were treated as having 'high exposure' and all others, as 'low exposure.' Duration of exposure to type of drinking water was based on length of residence in the census household prior to 1975. Odds ratios (OR) were calculated using logistic regression methods, adjusting for age, gender, tobacco use, and urbanicity. Bladder cancer risk was associated weakly in the general population with duration of exposure to municipal water. The association was limited to those who had smoked cigarettes. In ever-smokers compared with never-smokers with low exposure, the adjusted ORs for bladder cancer risk with increasing exposure were 1.3, 1.4, 1.4, 1.7, 2.2, 2.8, respectively, for 0, 1-10, 11-20, 21-30, 31-40, > 40 years' exposure duration. The ORs in smokers were not diminished after adjusting for smoking history and intensity. *Cancer Causes and Control* 1997, 8, 738-744

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Introduction

In the United States, about 192 million people are served by community water supplies, most of which rely on chlorine as a disinfectant.[1] Chlorine reacts with organics in water to produce halogenated organic compounds,[2] which generally are produced in higher concentrations in surface waters due to elevated levels of pretreatment organics.[3] Bioassays and *in vitro* studies suggest that some halogenated organic compounds in drinking water are mutagenic or carcinogenic.[4-7]

Since the late 1970s, epidemiologic investigations have attempted to assess whether chlorinated drinking water contributes to the incidence of bladder and other cancers. Several ecologic studies[8-12] have shown an association between bladder cancer mortality rates and source of drinking water or chlorination by-product levels. None, however, could control for well-established risk factors for bladder cancer, such as individual tobacco use.[13-20]

A number of case-control and cohort studies also have

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explored the association between cancer of the bladder and drinking water source.[21-32] A 1992 meta-analysis of seven studies,[33] which included a mix of mortality and morbidity investigations, yielded a relative risk (RR) estimate for bladder cancer from exposure to chlorinated water of 1.21 (95 percent confidence interval [CI] = 1.09-1.34). Only three of these studies,[25,27,28] and four reported subsequently,[21,30,31,34] examined the effects of tobacco use on the association between bladder cancer and chlorinated surface water. Of these, two[25,27] controlled for the population density or urbanicity of the subjects' residence, which are possible confounders of the association between drinking chlorinated surface water and bladder cancer.

One of the studies in the meta-analysis,[28] a cohort study in Washington County, Maryland (US) conducted with data from 1963 to 1975, found a twofold mortality risk for bladder cancer from chlorinated surface drinking water compared with unchlorinated groundwater. Our study, a population-based case-control study of incident bladder cancer in Washington, County, during a subsequent period, 1975-92, further explores the association between bladder cancer and exposure to drinking water from chlorinated surface waters and specifically considers tobacco use as well as urbanicity.

Materials and methods

Selection of cases and controls

In July 1975, a private census[35] of Washington County, Maryland obtained information on demographics, smoking history, source of drinking water, and other personal factors on nearly 90 percent of county residents. Cases were White residents enumerated in the census who had a first-time bladder cancer (ICD-9[36] code 188) reported to the county cancer registry between July, 1975 and the end of 1992. Non-Whites were excluded because race is a known risk factor for bladder cancer[13] and only a small percentage of county residents were non-White.[35] Three hundred cases were identified.

White controls were frequency-matched to cases on gender and five-year age groups through random selection from the 1975 census cohort. Eight controls per case (2,400) were selected to allow for exclusions for incomplete information regarding smoking history and drinking water source. The final study population consisted of 294 cases and 2,326 controls.

Exposure assessment

The 1975 census provided a cross-sectional survey of household drinking-water sources. The drinking-water survey information and a general description of Washington County drinking water have been reported elsewhere.[35] In brief, the census obtained the source of drinking water for each household in 1975 – whether municipal or from another source, including a well, spring, bottled water, or cistern using nonmunicipal sources. Nearly all municipal sources in 1975 were supplied by surface waters that had been chlorinated for more than 30 years.[35] Only one municipal source in a small town serving 279 households was chlorinated for less than 30 years, and that was for 10 years.[35]

In contrast, only six percent of nonmunicipal sources were chlorinated.[35] For these reasons, households reporting municipal sources were treated as receiving chlorinated drinking water from surface waters, and thus, as having relatively high exposure to chlorination by-products; households with nonmunicipal water sources were characterized as having low exposure.

Duration of exposure to municipal drinking water was derived from census information on the length of residence in a household served with municipal water at the time of the census. Exposure duration was categorized by 10-year intervals (1-10 years, 11-20 years, 21-30 years, 31-40 years, and more than 40 years).

Data and analysis

The 1975 census provided information for cases and controls on age, gender, marital status, education, employment status, cancer history, smoking history, residence, and source of drinking water. Individual smoking histories included whether participants had ever smoked cigarettes; whether they currently smoked cigarettes; and the number of cigarettes smoked daily by current smokers. Subjects also were categorized by area of residence: in Hagerstown (the only city in the county); suburban Hagerstown; other towns; or rural areas. Frequencies, crude and adjusted odds ratios (OR) and 95 percent confidence intervals (CI) were calculated for each of these factors, except age and gender.

The multivariate model included municipal water exposure in 10-year intervals, age, gender, smoking history, and residential location. ORs, CIs and trend tests, where applicable, were calculated by duration of exposure to municipal water for the total population, and for the population stratified by gender, and by smoking status. Associations were calculated with multiple logistic regression with the Logistic procedure in SAS.[37]

Results

Table 1 compares cases and controls by characteristics identified in the 1975 questionnaire. Cases and controls were nearly identical with respect to age and gender for which they were frequency-matched. Cases were more likely to be currently married, not to be employed, to have had less formal education, to have had a history of

Table 1. Characteristics of cases and controls, crude odds ratios (OR), adjusted ORs and 95% confidence intervals (CI) for incident bladder cancer associated with these characteristics,[a] Washington County, Maryland (status determined in 1975 census)

Characteristic in 1975	Cases (*n* = 294)	Controls (*n* = 2,326)	OR	Adj. OR	(CI)
Age (yrs)					
< 45	36	286			
45-54	51	407			
55-64	93	739			
65-74	80	633			
75+	34	261			
Gender					
Female	84	675			
Male	210	1,651			
Marital status					
Not married	49	557	1.0	1.0	—
Married	244	1,767	1.6	1.7	(1.2-2.4)
Employment status					
Not employed	158	1,212	1.0	1.0	—
Employed	134	1,102	0.9	0.9	(0.7-1.2)
Education level					
≤ 12 yrs	255	1,914	1.0	1.0	—
> 12 yrs	39	412	0.7	0.7	(0.5-1.0)
History of previous cancer					
No	272	2,194	1.0	1.0	—
Yes	18	113	1.3	1.3	(0.8-2.2)
Smoking status					
Never	82	912	1.0	1.0	—
Former	90	671	1.5	1.6	(1.1-2.2)
Current ≤ 24 cigarettes/day	73	459	1.8	1.9	(1.3-2.7)
Current 25+ cigarettes/day	41	234	1.9	2.2	(1.4-3.4)
Unspecified level or history[b]	8	50	1.8	1.9	(0.9-4.3)
Source of drinking water					
Nonmunicipal	79	722	1.0	1.0	—
Municipal (chlorinated)	215	1,604	1.2	1.2	(0.9-1.6)
Urbanicity					
Rural	74	692	1.0	1.0	—
Small town	28	238	1.1	1.1	(0.7-1.7)
Suburban Hagerstown	75	603	1.2	1.2	(0.8-1.6)
Hagerstown	117	793	1.4	1.4	(1.0-1.9)

[a] Odds ratios were calculated using logistic regression; adjusted ORs were adjusted for age (as categories) and gender.
[b] History refers to former *cf* current smoking status.

other cancers, to be former and current smokers, to be living in non-rural areas, and to use a municipal source of drinking water.

Residing in a home served with municipal drinking water at the time of the census was associated with an age and gender-adjusted OR for bladder cancer of 1.2 (CI=0.9-1.6) (Table 1). In the total population, the OR of exposure increased slightly with increasing duration of exposure to a municipal water source, after adjusting for age, gender, smoking level and history, and urbanicity (Table 2). When the analysis was stratified by gender, the association was observed only in men, with the adjusted OR increasing to 2.2 (CI = 0.8-5.1) among men who lived for more than 40 years in homes supplied with municipal water (*P* trend = 0.07). Additional adjustment for education and marital status did not appreciably modify the strength of the association between bladder cancer and municipal drinking water.

Table 3 presents adjusted ORs with increasing duration of exposure to municipal water by smoking status ('ever-smokers' and 'never-smokers'). The reference stratum was those who had never smoked and who reported a

Table 2. Odds ratios (OR) and 95 percent confidence intervals (CI) for incident bladder cancer by duration of residence with a municipal water source among men, women, and the total population,[a] Washington County, Maryland

Years residing with municipal water source	Men				Women				Total population	
	Cases	Controls	OR	(CI)	Cases	Controls	OR	(CI)	OR	(CI)
None	54	525	1.0	—	25	197	1.0	—	1.0	—
1-10	63	491	1.1	(0.6-1.9)	28	210	0.7	(0.3-1.7)	1.0	(0.6-1.5)
11-20	41	313	1.1	(0.6-1.9)	15	119	0.7	(0.3-1.8)	1.0	(0.6-1.6)
21-30	31	198	1.3	(0.7-2.5)	7	68	0.6	(0.2-1.6)	1.1	(0.6-1.8)
31-40	11	66	1.5	(0.6-3.3)	5	41	0.7	(0.2-2.2)	1.1	(0.6-2.2)
> 40	9	42	2.2	(0.8-5.1)	4	36	0.6	(0.2-2.2)	1.4	(0.7-2.9)
Unknown	1	16	—	—	0	4	—	—	—	—
P trend			0.07				0.48		0.33	

[a] Odds ratios were calculated using logistic regression, with adjustment for age, gender, smoking level and history (former *cf* current), and urbanicity, all categorized as in Table 1.

Table 3. Odds ratios (OR) and 95 percent confidence intervals (CI) for incident bladder cancer by duration of residence with a municipal water source and by smoking status,[a] Washington County, Maryland

Years residing with municipal water source	Never-smoker[b]				Smoker (past/present)			
	Cases	Controls	OR	(CI)	Cases	Controls	OR	(CI)
None	32	331	1.0	—	47	391	1.3	(0.8-2.2)
1-10	21	232	0.8	(0.4-1.6)	70	469	1.4	(0.8-2.5)
11-20	15	147	0.9	(0.5-1.9)	41	285	1.4	(0.8-2.5)
21-30	6	89	0.6	(0.2-1.5)	32	177	1.7	(0.9-3.2)
31-40	3	53	0.5	(0.1-1.5)	13	54	2.2	(1.0-4.7)
> 40	5	51	0.9	(0.3-2.3)	8	27	2.8	(1.0-6.9)
Unknown	0	9	—	—	1	11	—	—

[a] Odds ratios were calculated using logistic regression, adjusting for age, gender, and urbanicity, all categorized as in Table 1.
[b] Status determined in 1975 census.

Table 4. Odds ratios (OR) and 95 percent confidence intervals (CI) for incident bladder cancer by duration of residence with a municipal water source among men and women smokers (past or present),[a] Washington County, Maryland

Years residing with municipal water source	Male smokers				Female smokers			
	Cases	Controls	OR	(CI)	Cases	Controls	OR	(CI)
None	40	339	1.0	—	7	52	1.0	—
1-10	52	370	1.1	(0.6-2.1)	18	99	0.6	(0.1-2.9)
11-20	35	236	1.1	(0.6-2.2)	6	49	0.5	(0.1-2.3)
21-30	29	144	1.6	(0.8-3.2)	3	33	0.4	(0.1-2.2)
31-40	10	44	1.8	(0.7-4.5)	3	10	1.5	(0.2-10.9)
> 40	8	21	3.2	(1.1-8.6)	0	6	—	—
Unknown	1	10	—	—-	0	1	—	—
P trend			0.01				0.49	

[a] Odds ratios were calculated using logistic regression, adjusting for age, smoking level and history, and urbanicity, all categorized as in Table 1.

nonmunicipal source of drinking water. Among never-smokers, there was no association between bladder cancer and duration of exposure to chlorinated surface water, even at the highest cumulative municipal water exposures. In individuals with a smoking history, risk increased with lengthier exposures to municipal water, (adjusted OR for > 40 years = 2.8, CI = 1.0-6.9).

Table 4 shows adjusted ORs by duration of municipal

water source among men and women who had a history of smoking. Only men showed higher risks with increasing duration of exposure to municipal water. Male smokers with over 40 years' exposure had 3.2 times the risk of male smokers with other sources of drinking water (CI = 1.1-8.6), (*P* trend = 0.01). No association was seen for male or female never-smokers.

The data also were analyzed for potential exposure misclassification of the 'non-exposed' subjects by excluding those who had lived in their homes less than 10 years, which did not appreciably affect the results. The association among ever-smokers between bladder cancer and duration of exposure was not diminished by adjusting for smoking level and current smoking status.

Discussion

This study found a weak association between duration of exposure to chlorinated water and bladder cancer, consistent with several other studies.[21,28,34] In this study, the association was observed only among male cigarette smokers. Among those with no history of smoking, exposure to chlorinated surface drinking-water was unrelated to bladder cancer. These findings suggest that smoking may modify a possible effect of chlorinated surface water on the risk of bladder cancer.

Many of the strengths and limitations of this study were described previously in the IJsselmuiden *et al* study[35] of chlorinated drinking water and pancreatic cancer in Washington County, which used the same 1975 census. The strengths include obtaining cases from the county's oncology center, which draws patients from throughout the county as well as from neighboring areas. Moreover, any differences in case reporting were unlikely to be related to drinking water source or smoking history.

One potential ascertainment problem stems from the longitudinal (1975-92) case selection combined with the cross-sectional (1975) control selection. Some controls may have emigrated after 1975 and become 'cases' elsewhere. However, given both the low rates of emigration from Washington County and the similar proportions migrating among those receiving municipal and nonmunicipal water,[35] any underascertainment of cases probably did not appreciably bias the result.

Differential recall of exposure among cases and controls also was unlikely to have affected the result because exposure information was collected through a census given to all participants prior to diagnosis. In addition, the absence of occupational exposure information was unlikely to be of particular importance in Washington County, which has a relatively small industrial base.[35] Moreover, urban air pollution was likely to be limited in Washington County where the largest city, Hagerstown, had a population of about 35,000.[38] To the extent that urban environmental or lifestyle factors affected risk, the multivariate model adjusted for urbanicity.

Information on intensity of smoking among former smokers was not available. However, adjustment for current smoking levels and current or former smoking status did not markedly change the observed associations; it is therefore unlikely that further adjustment for past use levels would have had appreciable effects.

Other limitations of this study include several potential sources of misclassification in the water exposure measurement. The risk associated with drinking water exposure may depend on chlorination byproduct level,[25] chemical composition of the mixture, exposure duration,[28,30] and the amount of water consumed.[25]

In this study, there was limited information on levels and composition of chlorination byproducts in the drinking water during the exposure period (prior to 1975). Only the Hagerstown water source had been monitored for trihalomethanes, which are byproducts of chlorination. Water treatment changes made in 1979 likely decreased trihalomethane levels.[35] Thus, our limited information suggests that levels prior to 1975, during the study's exposure period, were greater than more recent levels.

There are also difficulties with inferring the duration of exposure from cross-sectional information on household drinking-water source and duration of residence in that household. Exposure duration was available only for the place of residence in 1975, and there was no information on prior or subsequent domiciles. Nonetheless, the stability of the Washington County population and the consistency of water source usage over time[35] support our use of the census instrument for estimating exposure.

Moreover, to the extent that individual water sources changed after 1975, these likely favored more use of chlorinated water sources. This would diminish the strength of the observed associations. In addition, when subjects with nonmunicipal water supplies who had resided in their 1975 houses less than 10 years were excluded from the analysis, the impact on the results was not substantial. Thus, it is also unlikely that residential exposures prior to those reported in the 1975 census appreciably affected the results.

We also had no information on the amount of water ingested by individual subjects. It is unlikely, however, that confounding by water intake could account for the positive interaction with smoking we observed. In order to explain the ORs we observed with duration of exposure in smokers, levels of drinking water consumption would have to be strongly associated both with risk and with duration of exposure in smokers. While the former is possible,[30] the latter is highly unlikely.

Of the four studies we are aware of that have explored the interaction between smoking and chlorinated water

risk,[21,25,31,39] only one[31] found smoking positively modified the risks of bladder cancer with chlorinated surface water. Available information does not account for these discrepancies. This may reflect, among other things, selection biases resulting from using cancer cases as controls[40] (in one study[21]) or differences in the composition of the chlorination by-product mixtures present in various surface waters. Additional studies of individual exposures to chlorinated surface water and tobacco are necessary to clarify, in the first instance, whether chlorination by-products pose a risk of bladder cancer, and secondly, whether and how tobacco use modifies such risk.

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